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Perspectives

Perinatal Programming of Neuropsychiatric Disorders

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The perinatal period is a period particularly sensitive to a variety of insults. During this period brain physiology and structure can be permanently altered, which may cause psychopathology to occur.[1–4] Substantial evidence suggests that many neuropsychiatric disorders originate during the developmental stage.[5,6] Animal studies show that the hippocampal-hypothalamic-pituitary-adrenal (HPA) axis can be programmed prenatally by nutrient restriction, exposure to synthetic glucocorticoids, stress, and infection. By contrast, the HPA can be programmed postnatally by neonatal stress, exposure to synthetic glucocorticoids, infection, and nutrient perturbations.[2,3,5–7]

The Concept of Developmental Origins of Health and Disease (DOHaD)

Environmental influences during development produce sustained effects on cellular function and physiology. Barker et al noted that low birth weight was associated with an increased risk of adverse outcomes in adulthood, such as coronary heart disease, stroke, high blood pressure, and type 2 diabetes.[8] Current evidence indicates that early phenotypes, such as low birth weight, are correlated with prenatal conditions that may elicit biological programming and reset physiological and metabolic responses, which persist in adulthood. Gluckman et al proposed the concept of DOHaD by observing the enduring effects of the fetal environment on physical health and disease in adulthood.[4,9] The DOHaD approach has become so popular that an international society has been formed, and this society is actively promoting research and collaboration in this area.

Perinatal Programming

The fetus is susceptible to environmental insults during the perinatal period. Programming is defined as the induction, silencing, or restriction of the development of somatic structures or a physiological system, which results in long-term effects. Glucocorticoids, the primary stress hormones, are critical for many aspects of normal development and are therefore prime candidates for perinatal programming.[1]

Perinatal programming effects are derived from environmentally induced alterations of maternofetal signaling. This may stimulate the fetal HPA axis to excessively amplify fetal glucocorticoid synthesis, as well as induce additional events in the fetus, including development of the immune and autonomic nervous systems. While these in utero responses may be adaptive in the short term,

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they ultimately may lead to an increased risk for various diseases, including neuropsychiatric disorders, in later life.

The HPA axis remains highly reactive and labile in early infancy and becomes organized between 2 and 6 months of age through transactions between the infant and caregiver. The quality of caregiving that the infant receives during early-life development predicts the emergence of the ability to self-regulate later. Sensitive caregiving is associated with better self-regulatory abilities and optimal functioning of the child's HPA system.[10]

Fetal Origin of Mental Diseases

Maternal adversities, such as stress, glucocorticoid exposure, infection, and nutrition deficiency, cause fetal growth retardation. Maternal infection can affect fetal brain development through mediators such as maternal cytokines, glucocorticoids, prostaglandins, and fever. Stress can be transferred from a pregnant mother to her fetus by various mechanisms such as transplacental transport of maternal stress hormones and through compromised fetal circulation.[5,6] These processes can have progressive and persistent consequences and lead to the development of postnatal brain dysfunctions, which are clinical manifestations of primary cerebral insults that occurred during early fetal development, long before the illness.

In animal studies, rats that received dexamethasone during the last trimester of pregnancy produced offspring that displayed anxiety-like behavior in adulthood. Similarly, prenatal stress in rats is associated with exaggerated stress responses in their offspring, which over time can produce adverse neuropsychiatric conditions. In addition, in mice, prenatal exposure to the influenza virus also induces a set of behavioral and pharmacological changes in adulthood, which are implicated in schizophrenia. Notably, maternal vitamin D deficiency represents a novel neurodevelopmental animal model for schizophrenia-like brain and behavioral pathology.[5,6]

In human studies, prenatal exposure to stressful events is associated with increased risk of schizophrenia, autistic disorder, posttraumatic stress disorder, and attention-deficit/hyperactivity disorder. Epidemiological studies in humans have provided substantial evidence suggesting that prenatal infection is associated with an increased risk for the development of psychiatric disorders, such as schizophrenia and autism. A growing body of epidemiological evidence cites maternal infection, not limited to a single viral or bacterial pathogen, as an important environmental factor that increases the risk of schizophrenia and related disorders in the offspring.[5,6]

Early Life Origin of Mental Diseases

The early postnatal period is a critical period when social interactions can affect the development of subsequent social behavior in adulthood.[10] Clinical studies have provided clear evidence for long-term neurobiological and neuroendocrine alterations after exposure to early adverse events.

Studies on animal models have shown that alterations in stress systems may compromise the development of emotion- and attention-regulation systems. Increasing evidence has shown that separation of rat pups from their mothers during the early postnatal period produces a permanent increase in anxiety-related behaviors, which is observed when the offspring are tested as adults. In addition, animal studies also provide evidence that augmented maternal care improves resilience to stress later in life. Rat pups that received better maternal care showed lowered activation of the HPA stress axis in response to challenges in adulthood.[2,7]

Clinical studies provide new evidence that the consequences of child abuse and family dysfunction early in life include a substantial increase in the incidence of substance abuse and depression. Similarly, early life stress also constitutes a major risk factor for posttraumatic stress disorder.[2,7,9]

Future Perspectives

Despite the mounting evidence provided by animal studies, neuroendocrine programming in humans remains largely unknown. Understanding the underlying mechanisms is essential for establishing appropriate intervention and thereby preventing or delaying neuropsychiatric disorders in adulthood. Immediate interventions during the acute phase of perinatal adversities may be one efficient strategy for the prevention of neurodevelopmental brain abnormalities in the offspring.[5] In addition, therapeutic interventions during the periadolescent period may represent another major strategy to reduce the incidence of brain dysfunctions following perinatal adversities.[5] Future works depend on research based on the molecular mechanisms underlying the relationship between perinatal adversities and neuropsychiatric disorders, as well as the coordinated development of targeted and effective intervention programs.

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